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Anti-Arthritic Compounds

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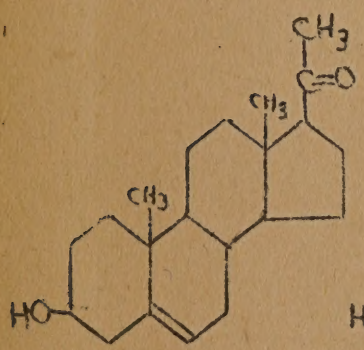
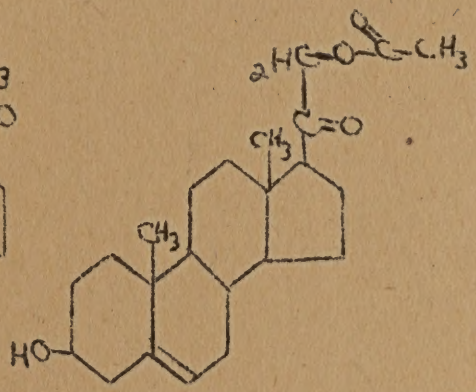
Previous reports have emphasized the fact that only steroids with an oxygen group at carbon 11 or 12 would be suitable precursors for anti-arthritic compounds (cf. report by Monroe E. Wall, 10/19/49 on "Chemistry of Sterols and Steroid Hormones" and memorandum of G. W. Irving, Jr. dated 1/24/50 on "Possible Sources of Biologically Important Sterols"). Recent developments have shown that steroids which are much simpler to prepare than cortisone have marked anti-arthritic effects. These compounds include pregnenolone (pregnene Δ^5, 3-ol, 20-one), artisone (pregnene Δ^5, 3-ol, 20-one, 21-acetoxy) and desoxycorticosterone (pregnene Δ^4, 3, 20-dione, 21-ol).

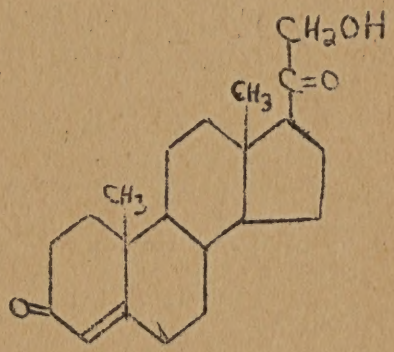
Pregnenolone



Artisone



Desoxycorticosterone



The last named compound is effective only when used in conjunction with ascorbic acid. Apparently, the newer anti-arthritics have fewer harmful side reactions than cortisone or ACTH. However, many more tests will have to be run before any really conclusive information will become available.

Of striking interest is the fact that these newer compounds are not oxygenated at carbon 11 or hydroxylated at carbon 17, these being structural features previously assumed absolutely essential for anti-arthritic activity. If recent reports are substantiated, it is obvious that an intensive search for these newer compounds will be made by various interested research groups.

These simpler compounds can be prepared in various ways. Oxidation of cholesterol, sitosterol, and stigmasterol results in the formation of intermediates from which the desired products can be made. The overall yields based on the starting sterols are very poor--at best 1 to 2% and often less. For example, mixed soya sterols (85% sitosterols - 15% stigmasterol) form an intermediate in 4% yield. This intermediate can be converted into pregnenolone in 40% yield. The overall process hence gives a recovery of only 1.6% and requires 12 steps.

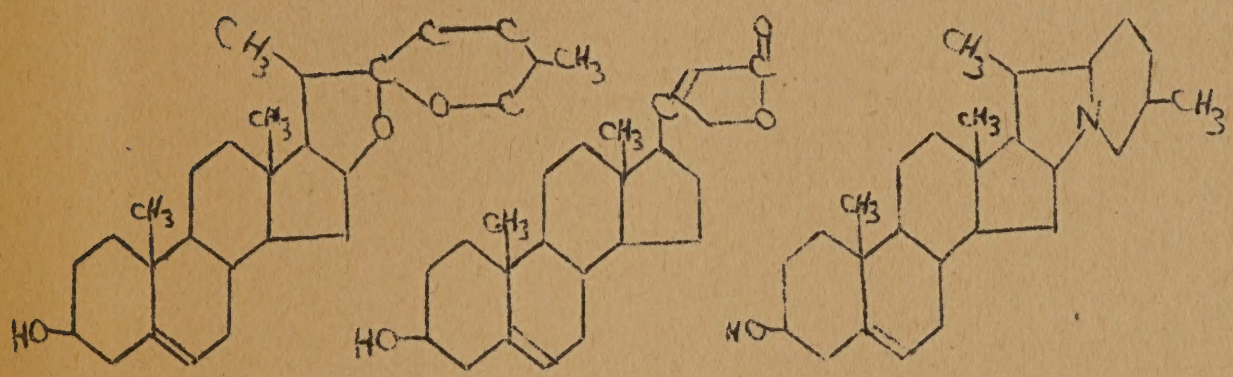
In sharp contrast pregnenolone can be prepared from a number of sapogenins in 50% yield by a process requiring only 4 steps. Up to the present time we have been concentrating on sapogenins with oxygen in the 11 or 12 positions. Under the circumstances it may be well to determine the total sapogenin content, both oxygenated and non oxygenated, of all specimens that are received.

Since our knowledge of the botanical distribution of sapogenins and similar compounds has increased since previous reports, it may be well to bring the subject up to date. The typical structures and brief descriptions of the botanical species in which the various compounds are found are therefore presented below.

Steroidal Sapogenin

Cardiac Steroidal Aglucone

Alkaloid Steroidal Aglucone



Steroidal sapogenins are found in a glucosidic form called saponins in plants belonging to the Liliaceae, Amaryllidaceae, and Dioscoriaceae. Typical examples are yucca, agave, and yam. It will be noted that these plants are all monocotyledonous. With the exception of digitalis, steroidal sapogenins have been found only in monocots. Saponins are found in many other plant families. These saponins do not have a steroidal aglucone but rather a triterpenoid residue. Unfortunately, steroidal and triterpenoid saponins are not clearly differentiated in the literature.

The cardiac agluconos are found as glucosides which have marked effects on the cardiac muscles of man and of animals. They are found in members of the Apocynaceae, Scrophulariaceae, Liliaceae, and Ranunculaceae including digitalis, strophanthus, squill, and lily-of-the-valley.

The alkaloid agluconos are found as glucosides in Solanum and Veratrum species including tomato and potato.

A few compounds have been found in each of the three groups which contain oxygen at C_{11} or C_{12}. Typical examples are botogenin (steroidal sapogenin) sarmentogenin (cardiac aglucone) and rubijervine (alkaloid steroidal aglucone).

The foregoing information has been presented in an attempt to bring up to date a rapidly changing research field. It seems probable at present that anti-arthritic compounds will not be limited to steroids oxygenated at C_{11} or C_{12}. As a consequence all naturally occurring compounds which can be readily converted to a pregnene or corticosterone structure should have considerable potentialities.